

Visualizing PCR amplification



ANALYSIS

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Few of us can successfully imagine a trillion of anything, so it's no surprise that the general public has trouble understanding how much a COVID PCR test amplifies the detected virus to determine whether a test is positive.

A previous post by Jennifer Cabrera and Alex Rodriguez, "Why mass PCR testing of the healthy and asymptomatic is currently counter-productive," discussed some of the problems with PCR tests. The short version is that documented studies show that PCR tests are too sensitive to identify live virus (infectious people) when they use a cycle threshold over 34, and almost all labs in the United States use at least 37, if not 40 or 42, cycles. The New York Times reported that these tests can produce 40% to 90% false positive results. (If you don't have a subscription you can read the summary from Apoorva Mandavilli's Twitter account.)

A PCR test repeatedly duplicates DNA (or RNA) sequences that are found in the sample and then checks to see whether the amount of replicated material exceeds some threshold. That means that in each cycle, the PCR doubles the amount of DNA/RNA in the sample. Unlike all the predicted exponential growth of COVID that never happened, repeated doubling is a real exponential function:

$$f(x) = 2^x$$

Here's a simple way to picture the process. Suppose you start with one fragment of COVID-19 RNA as shown here: (It may be hard to see depending on your screen size and resolution.)

Running this sample through a PCR cycle doubles the genetic material as seen here:



Running it four times doubles it two more times, growing to 16 pieces of RNA:

Running it 12 times grows the sample to 4,096 pieces. If you had trouble seeing the first dot, you should have no problems seeing them now (or at least noticing that the box appears to be gray).

Running a PCR test through 40 cycles results in 1,099,511,627,776 pieces of RNA. That's roughly 1.1 trillion. To put it into perspective, that 12-cycle graphic measures 10 inches x 10 inches on my computer monitor. Expanding that image for 40 cycles would require a monitor that's 163,840 inches wide… that's over 2.5 miles.

Instead of using something abstract like dots on a screen, let's repeat the exercise with a paperclip. Officemate sells a box of 100 No.1 paperclips. The box dimensions are roughly 2.81 x 1.7 x 0.9 inches. 10 boxes (1,000 paperclips) weigh just over 1 pound.

If we duplicate that paperclip for 40 cycles, we'd have 10,995,116,278 boxes weighing 1,099,511,628 pounds. That's over a half million tons. Ignoring space limitations, it would take 3,570 flights by a 747-8 cargo plane to move that much weight. (Another illustration of 1 trillion: using 1.03 pounds instead of 1 pound as the weight of each box would add another 107 fights.)

If you'd rather think of the size of the boxes, stacking them by their smallest dimension (0.9 inches), you'd have 15,618 miles worth of boxes. If you stack them vertically, you'll be higher than GPS satellites fly (12,550 miles). If you stack them horizontally, you'll get more than halfway around the earth (24,901 mile circumference).

The point is that duplicating something 40 times ends up so much bigger than the original sample that it's hard to imagine. It is roughly 1,000 times more material than you would get with 30 cycles.

The solution to this is, at the very least, to require test manufacturers to validate their tests by culturing a variety of samples, resulting in charts showing the cut-off for the detection of live virus. Then the cycle at which the test became positive (or at least whether it falls into a set of ranges) should be disclosed to the patient. This probably requires changes in the Emergency Use Authorizations (EUA) for the tests, and these changes should be pursued as urgently as the original EUAs were pursued at the beginning of the pandemic.